ACC.12
61st Annual Scientific Session & Expo
ACC-i2 with TCT innovation in intervention

E1685
JACC March 27, 2012
Volume 59, Issue 13

Prevention

AN ANTISENSE INHIBITOR OF APOLIPOPROTEIN C-III LOWERS FASTING PLASMA APOLIPOPROTEIN C-III AND TRIGLYCERIDE CONCENTRATIONS IN HEALTHY VOLUNTEERS

ACC Moderated Poster Contributions
McCormick Place South, Hall A
Sunday, March 25, 2012, 9:30 a.m.-10:30 a.m.

Session Title: Prevention: Clinical: Current Research in Lipidology
Abstract Category: 9. Prevention: Clinical
Presentation Number: 1190-529

Authors: *Vickie Alexander, Trish Novak, Nicholas Viney, John Su, Jennifer Burkey, Walter Singleton, Richard Geary, Isis Pharmaceuticals, Inc, Carlsbad, CA, USA*

Background: Apolipoprotein C-III (apoC-III) plays a pivotal role in regulating plasma triglyceride (TG) levels and is recognized as a CV risk factor. ISIS-ApoCIIIRx selectively inhibits apoC-III protein synthesis in the liver. This study assesses safety, tolerability, pharmacokinetics and pharmacodynamics of ISIS-ApoCIIIRx in healthy volunteers.

Methods: In this double-blind, single and multiple ascending-dose (MAD) study, healthy subjects, 18 to 55 years, were randomly assigned in a 3:1 ratio to receive ISIS-ApoCIIIRx or placebo (normal saline) administered as single or multiple subcutaneous (SC) injections at 50, 100, 200, and 400 mg (n=4/cohort). MAD cohort subjects received 6 doses over 4-weeks (a loading regimen of 3 doses the first week followed by once weekly dosing for 3 weeks).

Results: SC administration of all doses of ISIS-apoCIIIRx was generally safe and well tolerated. There were no clinically meaningful changes of liver tests or ALT elevations, and no serious adverse events. Pharmacodynamic results showed dose-dependent sustained reductions in total apoC-III and TG levels. Median percent change from baseline values in the 50, 100, 200 and 400 mg multiple-dose groups showed reductions of total apoC-III of 20, 17, 71, and 78%, and of TG of 20, 25, 43, and 44%, respectively, 1 week after the last dose. Reductions were sustained for at least 4 weeks after the last dose in the higher dose cohorts, consistent with the drug's long terminal elimination half-life. In addition, LDL-C values did not change while HDL-C values tended to increase in a dose-dependent manner. Pharmacokinetic results showed dose dependent exposure with time to maximum plasma concentrations between 2 and 4 hours and terminal elimination half life of about 2 to 4 weeks.

Conclusions: This first in man study demonstrates potent dose dependent, selective reduction of apoC-III and TG, two risk factors for CV disease. Based on the encouraging activity and tolerability seen in this study, phase 2 trials in patients with high TG are planned, both as a single agent and in combination. A selective inhibitor of apoC-III that can be used safely in combination with other agents could be of potential value in the treatment of CV disease.